

## CASE REPORTS

# Accelerated Atherosclerosis in a Cardiac Transplant Patient

ROBERT S. NITKIN, MD, FRCP(C), SHARON A. HUNT, MD, FACC,  
JOHN S. SCHROEDER, MD, FACC

Stanford, California

**A cardiac transplant patient with rapidly progressive graft atherosclerosis is described. This case demonstrates the accelerated nature of this disease and problems in diagnosis, as well as an unexpected and previously unreported lack of sensitivity of exercise thallium**

**scintigraphy in its investigation. This case also gives further support to the practice of routinely and frequently obtaining coronary arteriograms in the management of these patients.**

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The renewed interest in cardiac transplantation and improved patient survival rates since the introduction of cyclosporin have resulted in an increasing number of long-term survivors of this procedure. Experience with more than 300 heart and heart-lung transplantations performed at our institution has shown that one of the more serious long-term problems encountered is accelerated coronary atherosclerosis in the cardiac allograft. This process is detectable by coronary arteriography in approximately 40% of our patients at 5 years after transplantation. We report a case that is representative of this problem and illustrates how difficult its diagnosis may be owing to the lack of symptoms of myocardial ischemia.

## Case Report

**Clinical history and findings.** A previously healthy 24 year old male student presented in October 1981, complaining of a 5 day history of chest pressure accompanied by shortness of breath. Physical examination revealed mild respiratory distress, a supine blood pressure of 100/80 mm Hg and a pulse of 110/min. Jugular venous distension, cardiomegaly, a loud third heart sound, a grade 2/6 pansystolic murmur radiating to the axilla and crackles in both lung bases were noted.

Routine blood chemistry determinations, serum cholesterol and viral titers were normal. Electrocardiography re-

vealed sinus rhythm, narrow QRS complexes and QS complexes in leads V<sub>2</sub> and V<sub>3</sub> with inverted T waves in leads I, aVL and V<sub>6</sub>. Chest X-ray study showed cardiomegaly, pulmonary vascular redistribution and interstitial edema. At cardiac catheterization, left ventriculography showed globally decreased contractility (grade IV), with mild to moderate mitral insufficiency and an end-diastolic pressure of 25 mm Hg. Results of coronary arteriography were normal.

**Diagnostic studies.** At the time of biopsy, cardiac output was 3.3 liters/min and cardiac index was 1.8 liters/min per m<sup>2</sup>. Right heart pressures were moderately elevated and pulmonary vascular resistance was 2.4 units. Right ventricular endomyocardial biopsy revealed marked myocyte hypertrophy and disorganization, suggestive of a cardiomyopathy, with no evidence of myocarditis or infiltrative disease. Medical treatment for 3 months resulted in no improvement and the patient remained in New York Heart Association functional class IV and was accepted as a cardiac transplant recipient.

**Operative course.** On March 26, 1982, a 20 year old type O positive donor heart with human leukocyte antigen (HLA) typing A3-B7-BW6 became available. Routine orthotopic transplant procedure on the O positive recipient whose HLA type was A2-A11-BW4-BW6-BW35-BW57 was uneventful. Careful inspection of the donor heart at the time of transplantation revealed no abnormalities and no evidence of coronary artery disease. The heart removed from the patient weighed 550 g and all four chambers were hypertrophied. No coronary artery disease was detectable, and microscopic examination showed features consistent with cardiomyopathy.

**Postoperative course.** The patient was started on an immunosuppressive regimen consisting of cyclosporin and prednisone. The initial postoperative period was compli-

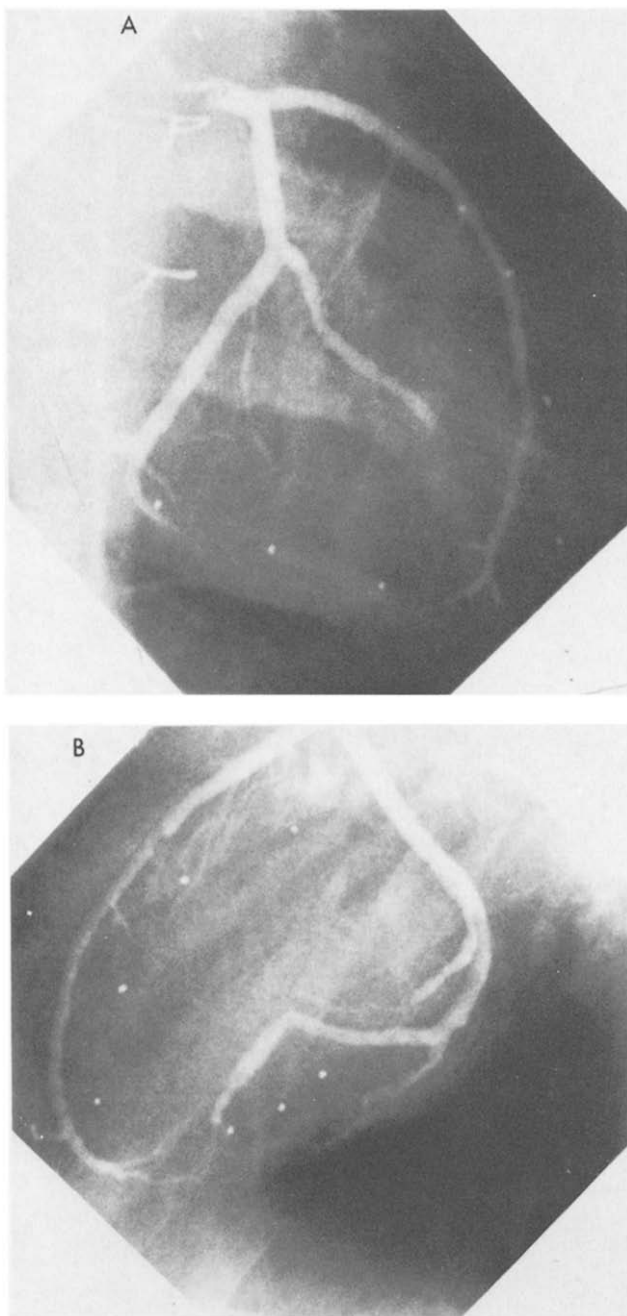
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**Address for reprints:** Robert S. Nitkin, MD, Cardiology Division, Falk Cardiovascular Research Center, Stanford, California 94305.

cated by several rejection episodes treated successfully with high dose steroids, a cytomegalovirus infection and a herpes zoster infection. By 8 weeks after transplantation, he was clinically well and returned to his studies.

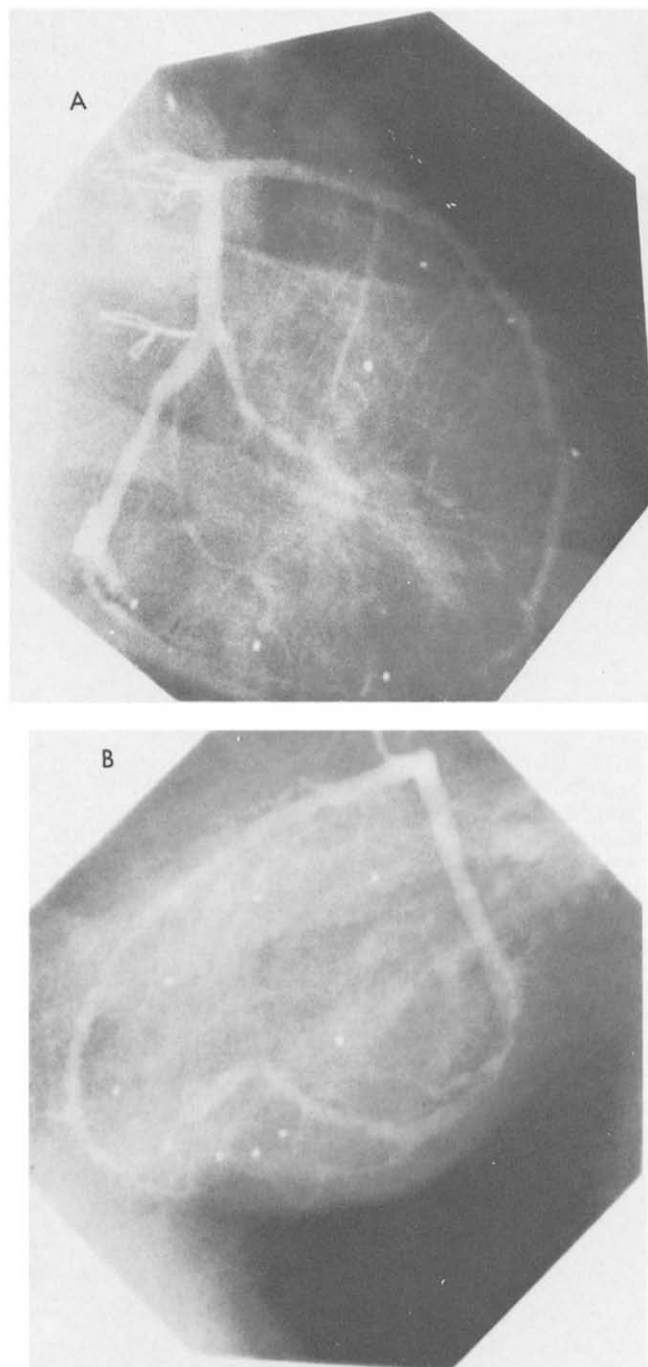
*On his first annual post-transplantation admission in March 1983, he was normotensive and his only medications included cyclosporin, prednisone (8 mg twice daily) and dipyridamole (Persantine). Cardiac catheterization revealed normal hemodynamic status, a normal ventriculogram and entirely normal coronary arteries. Fasting blood glucose of*

**Figure 1.** Left coronary artery angiograms in the right anterior oblique (A) and left anterior oblique (B) views obtained at the time of the second annual cardiac catheterization after transplantation.



98 mg/100 ml and all serum lipids were normal. Except for one further episode of mild rejection noted on routine surveillance right ventricular biopsy and treated with 100 mg daily of oral prednisone for 3 days with subsequent rapid tapering in September 1983, the patient remained free of complications and was able to continue all of the normal activities of daily living.

**Figure 2.** Left coronary artery angiograms in the right anterior oblique (A) and left anterior oblique (B) views obtained only 12 weeks after the study seen in Figure 1. Note the marked progression in the severity of the lesions.



**Long-term follow-up.** At his second annual admission in April 1984, cardiac catheterization again revealed normal hemodynamics; results of left ventriculography were normal except for trace mitral insufficiency. Coronary arteriography, however, revealed discrete 40 to 50% narrowing of luminal diameter in the first and second obtuse marginal branches of the circumflex artery (Fig. 1), as well as a 50 to 60% stenotic lesion at the terminal bifurcation of the right coronary artery. Diffuse disease of lesser severity was also noted in all three major coronary vessels.

On a routine exercise thallium study, maximal blood pressure, pulse and work load of 136/80 mm Hg, 140/min and 6 METS, respectively, were obtained and the test was terminated because of fatigue. The electrocardiogram and the immediate post-exercise and 4 hour delayed thallium images showed no evidence of ischemia. Biopsy revealed moderate acute rejection with myocyte necrosis, which was again treated with steroid therapy resulting in subsequent resolution. In view of the coronary artery disease, it was decided to obtain a repeat angiogram in 3 months.

On readmission 12 weeks later, the patient complained only of mild dyspnea on exertion. Fasting blood glucose and lipid studies remained normal. He was normotensive and new findings included a fourth heart sound, mild ankle edema and mild cardiomegaly with pulmonary vascular redistribution on X-ray study. The electrocardiogram remained unchanged. Diuretic drug treatment was instituted.

Cardiac catheterization on that admission revealed continued normal hemodynamics. Left coronary angiography showed discrete 80 to 95% stenotic lesions in the mid and distal left anterior descending coronary artery and first, second and third diagonal branches, with a totally occluded distal circumflex vessel. The first and second obtuse marginal branches contained localized 80 and 90% lesions, respectively (Fig. 2). The right coronary artery had a 95% discrete narrowing proximally. Right ventricular biopsy at that time again showed evidence of acute rejection for which the patient is currently being treated.

Because of the severity and rapidity of progression of his coronary artery disease, the patient was offered the option of elective retransplantation and is currently awaiting the availability of a suitable donor.

## Discussion

**Historical observations.** By the early 1970s (1), it became apparent that one of the major impediments to long-term survival in transplant patients was graft atherosclerosis. Possible causative factors that have been examined include age of the transplanted organ, histocompatibility of the match, type of immunosuppression used and clinical variables of the recipient such as underlying heart disease, number and degree of rejection episodes and the usual known risk factors of obesity, lipid status, glucose intolerance, family history, hypertension and smoking history. There has been no def-

inite correlation with any of these factors except donor age. More recently, a retrospective study from our institution (2) suggested that patients with underlying coronary artery disease as the cause of their initial transplantation are more likely to develop accelerated coronary artery disease than are those with normal vessels at the outset. However, this is not true in this isolated case.

**Diagnostic and therapeutic difficulties.** That the rapidity of this disease process is quite different from the coronary artery disease seen in patients without a cardiac transplant gives further support to the view that an immunologic mechanism is involved in this atherosclerotic process (3). Using a rat heterotopic heart transplant model, Lurie et al. (4) demonstrated that dipyridamole decreased immunologically induced arterial injury in this model; unfortunately, this has not proven to be as effective in human patients. The disease appears to develop despite this agent and because of cardiac denervation, all too often presents as silent myocardial infarction, sudden death or congestive heart failure (5).

Our patient's negative exercise thallium study is difficult to explain. Previous work (6) outlined some of the difficulties in interpreting thallium-201 images in patients who have undergone cardiac transplantation. Frequent false positive studies are anticipated, possibly related to myocardial ischemia induced by immunologically mediated small vessel disease. The reason for the false negative study in our case is unclear.

**Implications.** Until further work in this area gives some clues to the cause of accelerated atherosclerosis in cardiac allograft recipients and possible modes of halting it, we will continue to offer patients the option of repeat orthotopic cardiac transplantation, which does offer an acceptable alternative to patients with allograft failure (7).

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